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RESPIRATION-SYNCHRONOUS FLUCTUATIONS IN STROKE VOLUME, HEART RATE AND ARTERIAL PRESSURE IN HUMANS

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SUMMARY

1. Simultaneous recordings of beat-to-beat left cardiac stroke volume (SV, pulsed ultrasound Doppler), mean arterial pressure (MAP) and heart rate (HR) were obtained in ten healthy young adults during spontaneous respiration at supine rest, before and after cholinergic blockade by atropine (0·035 mg kg^{-1}).

2. Respiration-synchronous fluctuations in SV, HR, cardiac output (CO) and MAP were quantified by spectral analysis of the recordings of each of these variables.

3. Before atropine administration, respiration-synchronous fluctuations in HR and SV were prominent. The changes in HR and SV were inversely related and variation in SV was the main source of respiratory variability in CO. Respiration-synchronous fluctuations in MAP were mainly caused by variations in CO.

4. After cholinergic blockade, respiratory HR variations were eliminated, whereas the respiratory fluctuations in SV persisted. The fluctuations in CO and MAP increased. In this situation, mechanically induced variations in SV were not counteracted by inverse HR fluctuations and the influence on CO thus increased.

5. The main source of respiratory fluctuations in MAP in supine humans is thus variation in SV, while inverse, vagally mediated HR variations tend to reduce the fluctuations in CO and MAP.

INTRODUCTION

Spontaneous respiration is known to be accompanied by cardiovascular fluctuations. During the last few years both variations in heart rate (HR) and, to a lesser extent, variations in arterial pressure have been assessed by spectral analysis (Hyndman, Kitney & Sayers, 1971; Sayers, 1973; Rimoldi, Pierini, Ferrari, Cerutti, Pagani & Malliani, 1990). Respiration-synchronous variation is seen as peaks at the respiration frequency in the power spectral density curve of HR (Hyndman *et al.* 1971) and of systolic, diastolic (Furlan *et al.* 1990) and mean arterial pressure (MAP) (DeBoer, Karemaker & Strackee, 1985). Variations in arterial pressure induced by respiration are probably mainly caused by fluctuations in HR and left stroke volume (SV) (Dornhorst, Howard & Leathard, 1952*a*). At respiration frequencies between 0·15 and 0·40 Hz, the general view is that SV decreases and HR increases during inspiration (Robotham, Rabson, Permutt & Bromberger-Barnea, 1979; Saul, Berger, Chen & Cohen, 1989). If this is true, variations in HR and SV will

make counteracting contributions to cardiac output (CO) variation, thus reducing respiratory influence on arterial pressure. Atropine administration eliminates respiration-synchronous HR variability (Chamberlain, Turner & Sneddon, 1967; Fouad, Tarazi, Ferrario, Fighaly & Alicandri, 1984), whereas mechanically induced changes in SV are not changed to the same degree. Respiratory variations in CO and arterial pressure could thus increase after cholinergic blockade by atropine. In order to investigate this, we used non-invasive methods to make simultaneous recordings of the continuous beat-to-beat values of SV, HR and MAP in supine adults before and after cholinergic blockade by atropine. Respiration-synchronous fluctuations in these variables were quantified by spectral analysis and their phase angles were analysed. Preliminary results have been presented (Toska & Eriksen, 1993).

METHODS

Subjects

Ten healthy volunteers, four males and six females, aged 22–26 years, were studied. All were medical students, non-smokers, and in good physical shape. None was taking any medication. All were examined by a cardiologist (medical history, clinical examination and twelve-lead electrocardiogram) and none had any signs of cardiovascular disease. Written informed consent was obtained from all participants, and the study was approved by the local ethical committee.

Experimental design

Cardiovascular recordings of 5 min duration were obtained once before and once after cholinergic blockade by atropine. During recording sessions, the subjects lay comfortably in light clothing on a bench, and the ambient temperature was kept between 20 and 23 °C. The experiments were performed in the morning after an overnight fast. The subjects were all familiar with the experimental situation. Their respiration was spontaneous. The subjects were fully informed about the procedures and about the effects of atropine, but were not aware of the researchers' interest in their respiration. Mean respiratory frequency was roughly estimated during the recordings by silently counting for 60 s; no equipment was introduced to record the respiration continuously. The recordings were obtained before other experiments were carried out.

Instrumentation

Beat-to-beat SV was recorded using an ultrasound Doppler method (Eriksen & Walløe, 1990). A bidirectional ultrasound Doppler velocimeter, SD-100 (Vingmed Sound A/S, Horten, Norway) was operated in pulsed mode at 2 MHz, with a hand-held transducer. The ultrasound beam was directed from the suprasternal notch towards the aortic root and the sample volume range was adjusted so that measurements were made 1–2 cm above the aortic valve. The sample volume was positioned centrally in the aorta by searching for the highest obtainable velocity signal. An angle of 20 deg between the direction of the sound beam and the bloodstream was assumed in the calculations. In order to remove vessel wall and valve motion artifacts, together with any recorded diastolic movement of blood, the built-in high-pass filter in the SD-100 was set to remove signals originating from velocities below 0·275 m s^{-1}. The output of the SD-100 maximum velocity estimator and a three-lead surface electrocardiogram (ECG) were on-line interfaced to a microcomputer (Apricot XI ACT, Birmingham, UK) running a dedicated data collection and analysis program (BVA, Andiamo A/S, Oslo, Norway). In a separate session, the diameter of the rigid aortic ring was determined by parasternal sector-scanner imaging (CFM-750, Vingmed Sound A/S, Horten, Norway). On the assumption that the orifice is circular, this diameter was used to calculate the area of the aortic valvular orifice. SV was calculated by multiplying the value obtained by numerical integration of the recorded instantaneous maximum velocity during each R–R interval (the interval between successive R waves of the ECG) by the area of the orifice. The calculation is based on the assumption that the velocity profile in the aortic valvular orifice is rectangular and that this velocity is conserved as the central maximum velocity of a jet 3–4 cm downstream (Eriksen & Walløe, 1990).

Instantaneous HR was obtained from each R–R interval of the ECG signal and the beat-to-beat CO was calculated from the corresponding HR and SV values.

Finger arterial pressure was recorded continuously (2300 Finapres BP monitor, Ohmeda, Madison, WI, USA). The instantaneous pressure output was transferred on-line to the recording computer and beat-to-beat MAP was calculated by numerical integration. Arterial pressure obtained by this method has been shown to be in accordance with central, intra-arterial pressure in various situations (Parati, Casadei, Gropelli, Di Rienzo & Mancia, 1989; Imholz, Settels, van den Meiracker, Wesseling & Wieling, 1990).

Atropine medication

Atropine sulphate (Hydro Pharma, Oslo, Norway) was administered via an indwelling intravenous cannula. The initial dose was 0·015 mg kg^{-1} and repeated doses of 0·005 mg kg^{-1} were given at 3 min intervals until there was no further increase in HR after the injection. The doses used were 0·03 or 0·035 mg kg^{-1} (Chamberlain *et al.* 1967; Fouad *et al.* 1984).

Mathematical and statistical analysis

The fluctuations in SV, HR, CO and MAP were analysed using a statistical time series analysis programme (BMDP 1T: BMDP Statistical Software, Inc., Los Angeles, CA, USA). All signals were averaged and sampled on a beat-to-beat basis, triggered by the R wave of the ECG. The quality of the primary signals was observed continuously during the experiments. Furthermore, the primary recordings were visualized and carefully inspected to exclude any artifacts. Figure 2 displays a typical 5 min primary recording. Before calculations, the signals were converted into equidistant time samples by interpolation. The power spectra were obtained by fast Fourier transform and analysed using a bandwidth of 0·01 Hz. Since the sampling process was carried out at approximately 1 Hz, frequency components in the underlying biological signals below 0·5 Hz are correctly reproduced, whereas frequencies above 0·5 Hz will give rise to unwanted frequency components due to aliasing. The power spectra of the signals contained very little variance at frequencies above the respiratory frequency at approximately 0·3 Hz, making the presence of major signal components due to aliasing unlikely. Spectral power density was expressed in absolute terms, e.g. $(\text{beats min}^{-1})^2\ \text{Hz}^{-1}$ for HR. The phase between HR and SV was read from a smoothed cross-spectrum, at the frequency of the highest peak in the HR spectrum in the respiratory frequency range.

Mean respiratory frequency estimated by counting was in the range 0·22–0·33 Hz. We also found a prominent peak in the HR power density curve within this interval. The variance in the respiratory frequency interval was therefore quantified for each recorded variable by determining the area under the power spectrum curve in the interval 0·15–0·40 Hz. This value corresponds to the statistical sample variance in the signal after all variation at frequencies outside the interval of 0·15–0·40 Hz has been eliminated (Challis & Kitney, 1991). The statistical sample standard deviation (S.D.) of the signals in the respiratory frequency interval is accordingly the square root of this variance.

A theoretical value was also assigned to the contribution to the variance in CO from variations in HR and SV. The contribution from the SV variations was calculated as the S.D. of the SV signal in the respiratory frequency range multiplied by mean HR. In the same manner, the contribution from the HR variability was calculated as the S.D. of the HR signal in the respiratory frequency range multiplied by mean SV. To combine these two values with the resulting S.D. of CO in the frequency range, the phase between the separate variations in SV and HR must also be taken into account. If the values are regarded as vectors, the following will be true:

$$\overrightarrow{\text{S.D.(CO)}} = \overrightarrow{\text{S.D.(HR)}} \times \overline{\text{SV}} + \overrightarrow{\text{S.D.(SV)}} \times \overline{\text{HR}}.$$

The statistical significance of changes was tested by the Wilcoxon signed rank sum test.

RESULTS

Due to technical difficulties with the ultrasound Doppler apparatus, we were not able to obtain adequate recordings of SV in one subject (T.K.) after administration of atropine. This subject is, however, included in the analysis of MAP and HR.

The beat-to-beat variations in the recorded variables are illustrated in Fig. 1 which shows a sequence of simultaneous MAP, CO, SV and HR recordings in one

representative subject (L.J.) during a few respiratory cycles. In the control state (left-hand panels), HR increases as SV decreases, resulting in a small decrease in CO and a decrease in MAP. After cholinergic blockade (right-hand panels), HR is almost constant and SV decreases simultaneously with CO and MAP.

Two complete 5 min primary recordings of MAP, CO, HR and SV from the same subject before and after atropine are shown in Fig. 2 and the corresponding spectra in the interval 0·05–0·4 Hz are shown in Fig. 3.

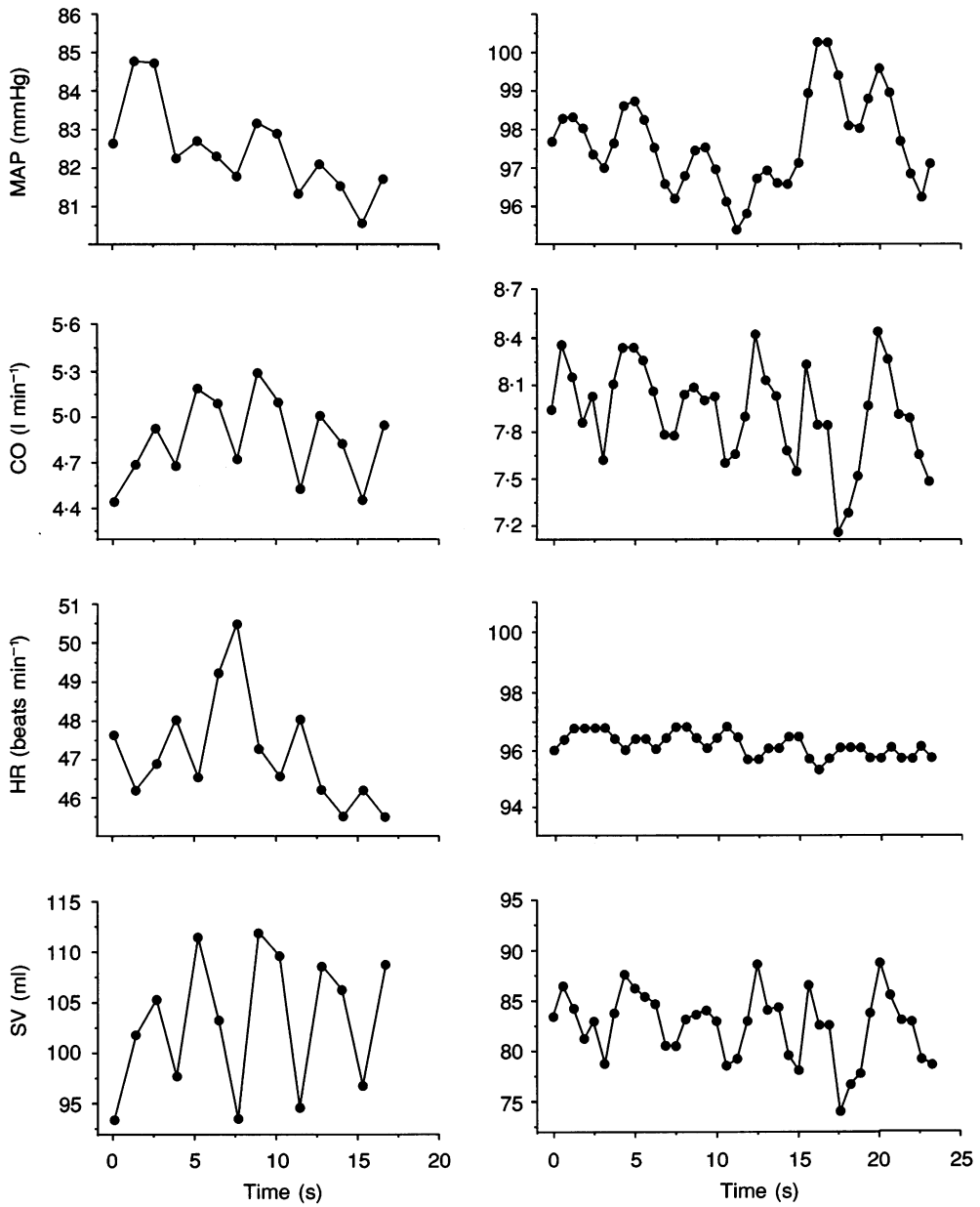

Fig. 1. A sequence of simultaneous MAP, CO, SV and HR recordings in one subject (L.J.) before (left-hand panels) and after (right-hand panels) atropine administration.

The administration of atropine caused a substantial increase in HR and a decrease in SV, resulting in an increase in CO and MAP. The respiration-synchronous variations in HR largely disappeared, whereas there were still considerable beat-to-beat variations in SV, CO and MAP.

Table 1 summarizes the mean values of MAP, CO, SV and HR, before and after cholinergic blockade.

Before atropine administration, the power spectrum of SV showed a prominent peak at the respiratory frequency in all subjects. All but one subject (M.K.) also showed a prominent peak at the respiratory frequency in the HR power spectrum. In all but two subjects (M.K. and R.J.), the respiration-synchronous variations in

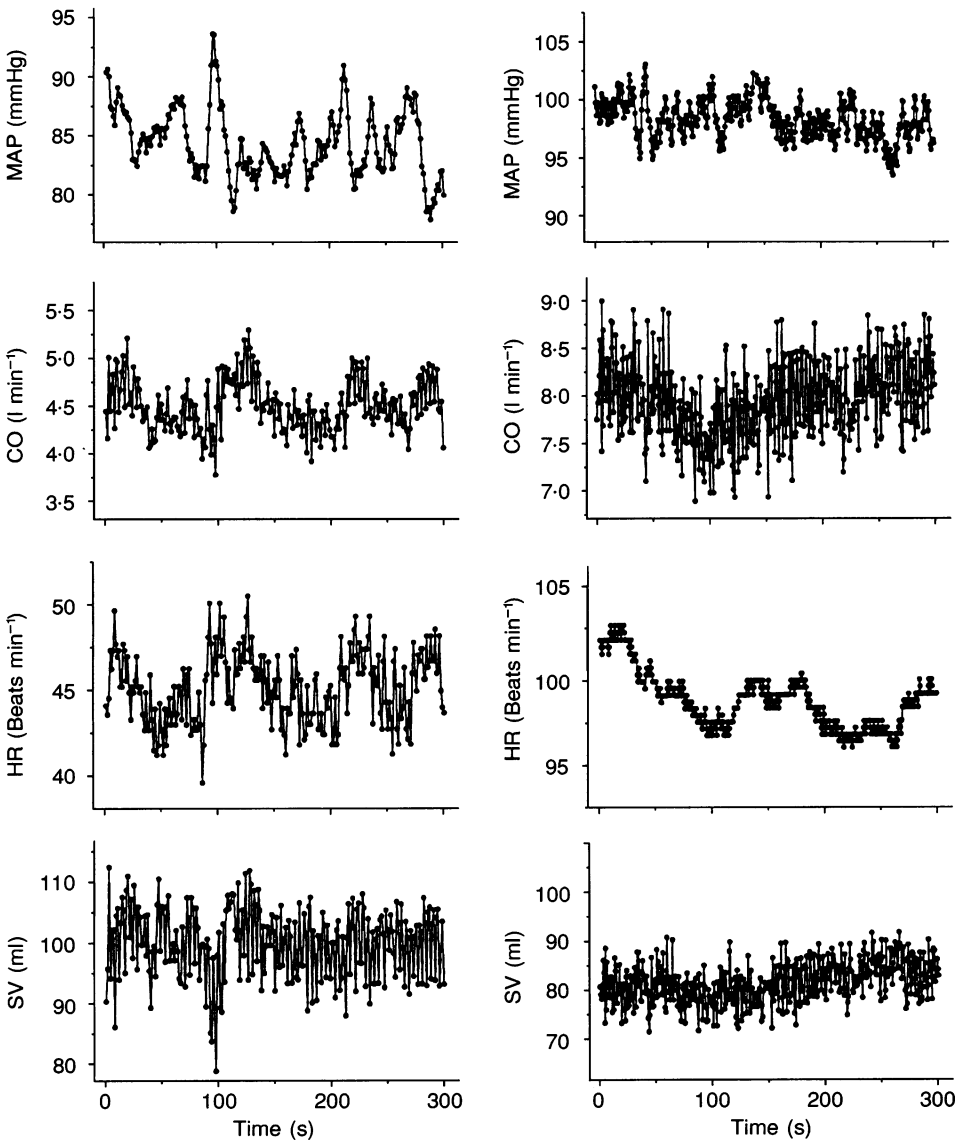

Fig. 2. A primary recording of MAP, CO, HR and SV from one representative subject (L.J.) before (left-hand panels) and after (right-hand panels) atropine administration.

MAP and CO increased after cholinergic blockade by atropine ($P = 0{\cdot}02$). This is shown in Fig. 4.

In Fig. 5 fluctuations in the CO recordings are compared to the theoretical contributions from the variation in SV and HR before (Fig. 5*A*) and after (Fig. 5*C*) atropine administration (see Methods). In the control situation, the sum of the theoretical contributions of SV variation and HR variation is greater than the CO variation, indicating an inverse contribution from SV and HR. The inverse relationship between SV and HR was also confirmed by the phase angle between the two signals, which was about 180 deg (Fig. 5*B* and *D*), while the coherence between the two signals was above 0·9.

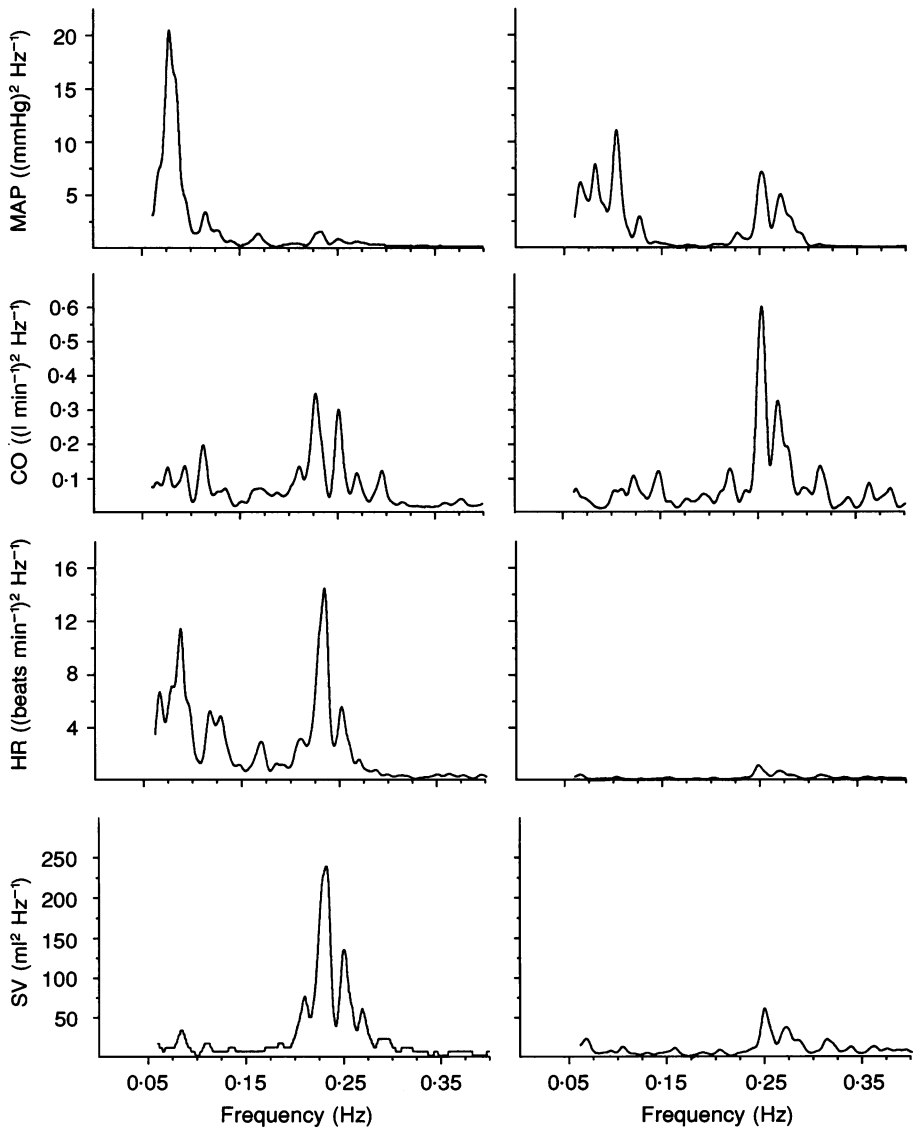

Fig. 3. Power spectral density curves in the interval 0·05–0·4 Hz from the recordings shown in Fig. 2.

TABLE 1. The mean values of MAP, CO, SV and HR before and after cholinergic blockade

	MAP (mmHg)		CO (l min^{-1})		SV (ml)		HR (beats min^{-1})	
Subject	Before atropine	After atropine	Before atropine	After atropine	Before atropine	After atropine	Before atropine	After atropine
H.G.	80	95	4·2	5·3	70	50	60	105
R.J.	85	97	3·7	5·8	73	57	51	102
L.J.	85	100	4·5	7·9	99	81	45	98
H.V.	70	102	4·3	6·3	75	64	57	98
L.M.	75	105	5·0	9·2	85	66	59	139
T.K.	67	79	3·9	—	70	—	55	105
P.L.	69	85	5·0	6·2	84	70	60	88
E.L.	68	98	4·4	7·1	80	72	55	98
M.K.	65	96	3·2	6·1	70	60	45	101
K.Y.	85	120	4·8	7·3	85	64	56	114
Mean	75	98	4·3	6·8	79	65	54	105

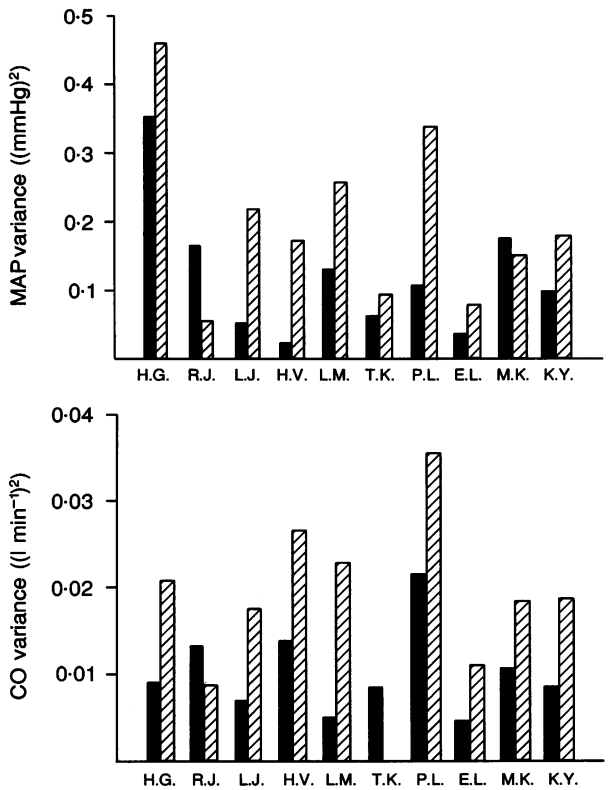

Fig. 4. Variance in the respiratory frequency interval in mean arterial pressure (MAP, upper panel) and cardiac output (CO, lower panel) before (filled columns) and after (hatched columns) cholinergic blockade.

DISCUSSION

The main findings of this study are that there is an inverse relationship between respiration-synchronous changes in SV and HR and that the main source of

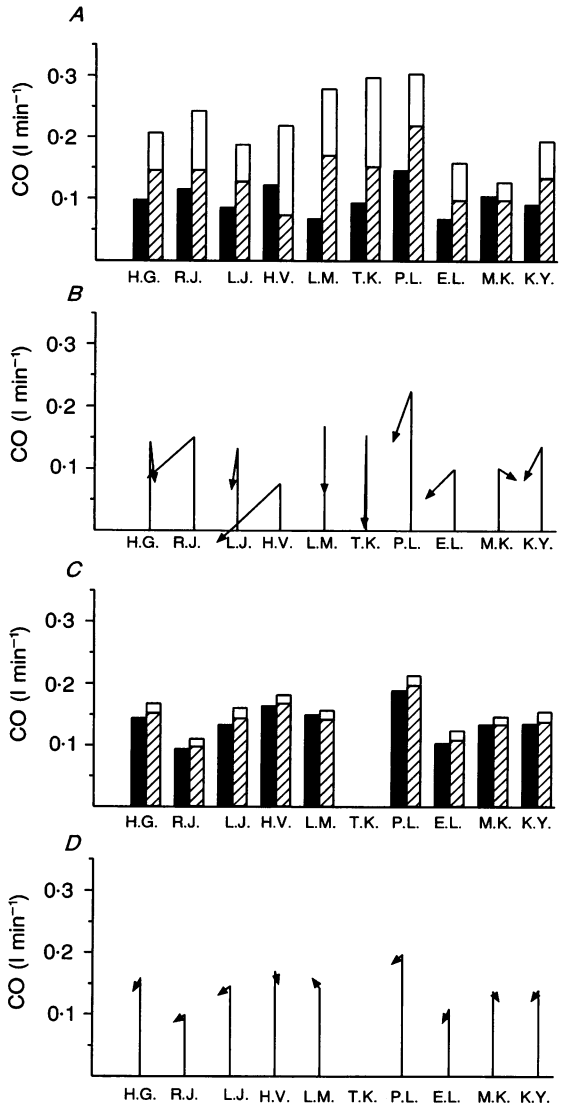

Fig. 5. Variation in CO (■) and the theoretical contribution to CO variation from variation in HR (□) and SV (▨) (see Methods). Values before (*A*) and after (*C*) atropine administration are shown. Before (*B*) and after (*D*) atropine the SV and HR variations are represented as vectors and the angle between them is the phase angle between the SV and HR signals. The vertical vector is the SV variation. Thus, the vector for the respiratory variations in CO would be represented by a vector drawn from the start of the vertical vector to the tip of the HR vector. In L.M. and T.K. the phase angle is 180 deg.

respiration-synchronous fluctuations in MAP is variation in SV (Fig. 5). This is confirmed by the fact that respiration-synchronous fluctuations in MAP increase after the HR changes are eliminated by cholinergic blockade.

Respiratory activity perturbs cardiovascular variables through a number of direct and indirect mechanisms and the relationship between respiration and both HR and SV is dependent on a number of factors, including species, posture,

haemodynamic stress, respiratory frequency and depth (Saul, Berger, Albrecht, Stein, Chen & Cohen, 1991) and age (Hellman & Stacy, 1976). Our findings may, therefore, only be representative for the population studied, i.e. young, healthy humans in good physical shape and the given situation, i.e. supine, unstressed subjects during quiet, spontaneous respiration.

Respiration-synchronous variation in MAP

MAP rather than systolic and diastolic pressures, was used to represent arterial pressure, both because MAP may be the most important input variable to the baroreflexes (Sanders & Ferguson, 1989) and also because MAP is influenced by changes in both SV and peripheral resistance. Furthermore, distortion of the pressure waveform caused by pulse-wave transmission and reflection in the brachial arteries may affect the systolic and diastolic pressures recorded in the finger. However, such waveform distortions are cancelled in the process of beat-synchronous averaging for calculation of MAP.

It is generally believed that inspiration causes a decrease in arterial pressure in humans (Dornhorst *et al.* 1952*a*; Wise *et al.* 1981). However, some authors describe the opposite relationship (Shepherd & Vanhoutte, 1979). It is also well known that during spontaneous respiration, HR increases during inspiration. Our results indicate that fluctuations in MAP reflect variations in CO (Fig. 4). Indeed, Fig. 1 illustrates that as HR increases, there is a decrease in SV, CO and MAP. Therefore it seems that in resting supine young adults the inspiratory increase and the expiratory decrease in HR reduce the arterial pressure variations caused by the respiration-synchronous variations in SV. However, an increase in the respiration-synchronous variation in MAP was observed in only eight out of ten subjects after cholinergic blockade. One of the atypical subjects (M.K.) had very small respiration-synchronous HR fluctuations before blockade; in this subject, the changes produced by atropine administration were thus small and the variability in MAP decreased only slightly. In the other atypical subject (R.J.) the phase between SV and HR was atypically 130 deg. In this subject, the contribution to the CO variation made by the respiratory-related changes in SV also decreased after atropine administration, indicating that HR changes may have influenced the SV changes more in this subject than in the others (see Fig. 4).

Few studies have described respiratory effects on arterial pressure variability after cholinergic blockade in humans. Kitney, Fulton, McDonald & Linkens (1985) stated that after atropine administration 'respiratory effects were still evident within the arterial pressure spectrum'. In another study, no change in MAP variability was seen in cat or man after atropine administration (Mancia *et al.* 1985). In a study of long-term variability in HR and blood pressure, atropine caused a decrease in the variability of diastolic arterial pressure, but no significant change was observed in the variability of systolic arterial pressure 'indicating that the SV variations were still present after cholinergic blockade' (Clement, De Pue, Jordaens & Packet, 1985). In these two latter studies the total variability in arterial pressure was assessed and therefore it was not possible to distinguish the respiratory-dependent variation.

Although our findings are compatible with established physiological findings in humans, there seems to be much confusion with regard to respiratory variation in HR and in arterial pressure and many authors seem to suggest that both are

expressions of the parasympathetic influence on the heart (Furlan *et al.* 1990; Rimoldi *et al.* 1990). Our findings indicate the opposite, as the vagally mediated HR fluctuations reduce the respiratory fluctuations in MAP. In many investigations using spectral analysis of cardiovascular variables the subjects were dogs. In this species, atropine administration causes a clear reduction in respiration-synchronous variation in arterial pressure (Rimoldi *et al.* 1990). This interspecies difference is explained by the much greater respiratory-dependent HR variation in dogs, such that HR fluctuations are the main source of variation in arterial pressure and there is only minor mechanically induced SV variation (Saul *et al.* 1991). Hence in this area experimental findings from dogs cannot be applied directly to human physiology.

Respiration-synchronous variation in SV

Spectral analysis of fluctuations in SV has not previously been reported in humans, probably because no method was available for recording beat-to-beat SV reliably over long periods of time. The ultrasound Doppler method might in itself give rise to apparent respiration-synchronous variations in recorded SV, mainly because inspiratory movements induce a downward movement of the heart. However, if our method is used, this will only have a minor effect because the sample volume is positioned in the middle of the ascending aorta, 1–2 cm above the aortic valve, and the central maximum velocity is conserved in a 3–4 cm long jet downstream from the aortic orifice (Eriksen & Walløe, 1990). Thus, the same, maximum velocity is recorded even if the heart moves downward during inspiration. Our results must thus reflect real, physiological fluctuations.

Guz, Innes & Murphy (1987) used ultrasound Doppler and found that SV fell during inspiration and rose during expiration. They also reported that breathing was associated with larger SV variations when HR was held constant by an implanted pacemaker.

The decrease in SV during normal inspiration is partly caused by a reduced cardiac filling time as HR increases, but the main causes of the respiration-synchronous variation in SV are changes in intrapleural pressure and direct mechanical interactions between the right and the left part of the heart (Dornhorst, Howard & Leathard, 1952*b*; Guntheroth & Morgan, 1967; Schrijen, Ehrlich & Permutt, 1975; Robotham, 1979).

Respiration-synchronous variation in HR

The respiration-synchronous HR changes are partly ascribed to a feedforward regulation coupled to the respiratory regulation (Katona, Poitras, Barnett & Terry, 1970) or to reflexes induced by pulmonary stretch receptors, and partly to a feedback regulation through arterial baroreflexes (DeBoer, Karemaker & Strackee, 1987). Both mechanisms can explain the inverse relationship between HR and SV seen in this investigation. It has been claimed that respiratory-related change in HR is critically dependent on the level of baroreceptor stimulation of vagal nuclei, and very often respiratory HR variations are used as an indicator of 'vagal tone' (Akselrod, Gordon, Madwed, Snidman, Shannon & Cohen, 1985). In our study, one subject had very small respiration-synchronous variation in HR (M.K.). She was endurance trained and had a low resting heart rate of 45 beats min^{-1}, indicating a high firing frequency in the vagal nerves to the sino-atrial node. Despite this, there

was no evident high frequency peak in her HR power spectrum. This indicates that the high frequency peak in the power spectrum cannot be regarded as an absolute sensitive indication of 'vagal tone' (Kollai & Mizsei, 1990).

Respiration-synchronous variation in peripheral resistance

Respiratory periodicity has been found in muscle sympathetic nerve recordings (Hagbarth & Vallbo, 1968; Eckberg, Nerhed & Wallin, 1985) and this might introduce respiration-synchronous fluctuations in total peripheral resistance (TPR). We have not assessed respiratory-related variations in TPR from our recordings. The calculation of TPR by dividing MAP by CO is not to be relied upon during rapid changes in arterial pressure (Laskey, Parker, Ferrari, Kussmaul & Noordergraf, 1990) and the calculation will be vulnerable to zero-point errors and non-linearities in the methods used for the primary recordings of CO and MAP. Respiratory fluctuations in peripheral resistance should therefore be investigated instead by measurements of flow in peripheral vessels.

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